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Marijuana Use in Pregnancy: A Review

Rebecca Thompson, MD[*], **Katherine DeJong, MD**[†], **Jamie Lo, MD**[‡]

[*]Postgraduate Year 1, Obstetrics-Gynecology Resident, Oregon Health & Science University, Portland, OR

[†]Postgraduate Year 3, Obstetrics-Gynecology Resident, Oregon Health & Science University, Portland, OR

[‡]Assistant Professor, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR

Abstract

Importance: Marijuana is the most commonly used dependent substance in pregnancy. The main active chemical of marijuana (delta-9-tetrahydrocannabinol [THC]) readily crosses the placenta, and cannabinoid receptors have been identified in fetal brain and placenta. As a result, prenatal marijuana use could potentially have detrimental impact on fetal development.

Objective: This review aims to summarize the existing literature and current recommendations for marijuana use while pregnant or lactating.

Evidence Acquisition: A PubMed literature search using the following terms was performed to gather relevant data: “cannabis,” “cannabinoids,” “marijuana,” “fetal outcomes,” “perinatal outcomes,” “pregnancy,” “lactation.”

Results: Available studies on marijuana exposure in pregnancy were reviewed and support some degree of developmental disruption, including an increased risk of fetal growth restriction and adverse neurodevelopmental consequences. However, much of the existing prenatal marijuana research was performed in the 1980s, when quantities of THC were lower and the frequency of use was less. Additionally, most human studies are also limited and conflicting as most studies have been observational or retrospective, relying primarily on patient self-report and confounded by polysubstance abuse and small sample sizes, precluding determination of a causal effect specific for marijuana. Given the paucity of evidence, it is currently recommended to avoid using marijuana while pregnant or when breastfeeding.

Conclusion and Relevance: There is a critical need for research on effects in pregnancy using present-day THC doses. Once the adverse perinatal effects of marijuana exposure are identified and well characterized, patient education and antenatal surveillance can be developed to predict and mitigate its impact on maternal and fetal health.

Target Audience: Obstetricians and gynecologists, family physicians.

Correspondence requests to: Jamie Lo, MD, 3181 SW Sam Jackson Park Rd, Mail Code L458, Portland, OR 97239. Loj@ohsu.edu.

All authors, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations relevant to this educational activity.

Learning Objectives: After participating in this activity, the provider should be better able to counsel patients regarding prenatal marijuana use; assess patients during pregnancy for marijuana use; and explain recommendations regarding marijuana use while breastfeeding.

Marijuana is the no. 1 dependent substance used in pregnancy,[1,2] with up to half of users continuing their use while pregnant.[3–5] This results in up to 34% of pregnancies impacted, which is significant.[6–9] The high prevalence of prenatal marijuana exposure is likely due to its perceived safety in pregnancy, the recent legalization trend,[3–5,10] and its appeal in potentially providing relief for common pregnancy ailments such as nausea. Given that the active ingredient of marijuana (delta-9-tetrahydrocannabinol [THC]) readily crosses the placenta and that studies have demonstrated expression of cannabinoid receptors in fetal brain and placenta,[11–13] there is concern for adverse fetal outcomes.[14–16] The available published studies on marijuana exposure in pregnancy support some degree of developmental disruption associated with maternal marijuana use. Maternal marijuana use has been associated with stillbirth, fetal growth restriction, and fetal neurodevelopmental consequences.[14,16–22]

Currently, there is a paucity of well-designed studies that assess the effects of prenatal exposure to marijuana on fetal and placental health outcomes.[2,23,24] This is partly because marijuana has been considered an illicit drug, and thus there is scarce information on its physiological effects in pregnancy. More importantly, existing studies are conflicting because most human studies are confounded by polysubstance abuse, small sample size, lifestyle issues, self-reporting, and recall bias.[2,24] Also, unlike alcohol where a shot, a glass of wine, and a beer have roughly the same amount of alcohol based on the volume they contain, there is no such equivalency for marijuana because different strains of marijuana plants and the route used vary in potency. There is also no reliable method to quantify the amount of marijuana used through biological sampling[2,24]; thus, human studies rely on patient self-report contributing to the heterogeneity in reported results. The pattern of marijuana use is also changing, with more current users using daily or nearly daily compared with previously.

Moreover, most of the literature reflects marijuana exposure almost exclusively through smoking, with few reports on more contemporary routes of administration.[25–29] Alternative vehicles for marijuana delivery, such as edibles, have become more popular especially in states with legalized marijuana use; increased interest can be attributed to perceptions shared by users that edibles and other forms of marijuana are a discreet and more convenient way to consume marijuana while avoiding the harmful toxins and health risks associated with smoking.[30] However, the effects of contemporary marijuana products on pregnancy outcomes are difficult to study because they often lack consistency in formulation and labeling, resulting in potentially greater THC exposure; additionally, they also have higher quantities of THC than in the 1980s when much of the marijuana research, including animal studies, was performed.[31,32] Currently, the state of Washington’s legal cannabis market has flower products with THC concentration greater than 20% THC and extract products with greater than 60% THC.[33] By comparison, national estimates of average THC levels in the United States in 2010 ranged from 8% to 13%.[34,35]

Overall, with the burgeoning marijuana movement in the United States and the momentum behind marijuana law reform, there is a critical need to adequately understand marijuana's effect on placental and fetal development for health care providers to better counsel pregnant patients and to develop targeted therapeutics for pregnancies at risk in women who are unable to abstain from drug use in pregnancy. This review is intended to offer health care providers an understanding of the existing literature and current recommendations for pregnant or lactating women who are using marijuana. The term *marijuana* is used throughout this article to represent cannabis use as a whole.

LEGALIZATION TREND AND HEALTH POLICY

In 2012, Colorado and Washington became the first 2 states to legalize marijuana. As of this writing, a total of 33 states and the District of Columbia have enacted laws legalizing marijuana at the state level for recreational and/or medical purposes. As such, nearly 25% of the US population lives in states that have passed ballot initiatives to allow businesses to produce and sell marijuana. The consequences of this legalization trend on health, public safety, and social equity will be in part shaped by decisions made regarding production, prices, and enforcement of regulations.

A new bill, H.R. 420, titled the "Regulate Marijuana Like Alcohol Act," has been filed in the House. If passed, this bill would remove marijuana from the federal Controlled Substances Act. There has also been movement to transfer marijuana enforcement authority from the Drug Enforcement Administration to a renamed Bureau of Alcohol, Tobacco, Marijuana, Firearms, and Explosives. Under current law, the Treasury and Health and Human Services departments share jurisdiction over alcohol and tobacco packaging and labeling; this provision would extend similar packaging and labeling authority over marijuana products.

CANNABIS

Marijuana, also known as cannabis, is derived from plants of the genus *Cannabis,* a member of the Cannabaceae family, of which *Humulus* (or hops) is also a member.[36] While the exact taxonomic differentiation of marijuana remains an area of active debate, perhaps more clinically relevant are the chemical differentiations of marijuana, or chemotypes. Phytocannabinoids are the pharmacologically active compounds found within marijuana that correspondingly interact with cannabinoid receptors. Marijuana chemotypes are determined by the concentrations of the 2 most studied cannabinoids found within marijuana, tetrahydrocannabinolic acid and cannabidiolic acid, which are then decarboxylated to their active analogs, THC and cannabidiol (CBD).[37] Marijuana chemotypes include THC type, hybrid or intermediate type, and CBD type.[29] Traditionally, THC-type marijuana strains have been considered drug types, and CBD-type strains have been cultivated for extraction of fiber. This differentiation lacks relevance, as CBD is in fact pharmacologically active, although it lacks the psychoactive attributes with which THC is associated.[29,38] When considering the health effects of marijuana, clinicians must consider THC and CBD independently, as cannabinoid products increasingly contain one or the other, and patients may view these cannabinoids as distinct entities. Understanding the differences between the

chemical properties of these cannabinoids will enable the provider to deliver comprehensive counseling to patients and will be discussed in the following sections.

Marijuana has an extensive medicinal history. The plants are native to Western and Central Asia and were integrated into the Ayurvedic medicinal culture of Ancient India and cultivated for medicinal purposes as early as 900 BC. There are descriptions in Egyptian medical papyri of marijuana vaginal suppositories, which it is theorized were used as obstetric aids. By the time marijuana came to the attention of the European scientific community, its analgesic, myorelaxant, and psychotropic effects, among others, had been well described.[36] In the 1830s, an Irish physician, O'Shaughnessy, described the pharmacological properties of marijuana to the Western medical community after observing its use in India.[39,40] Following this debut, several European physicians conducted pharmacological experiments on marijuana. Subsequently, marijuana research was largely abandoned throughout the early and mid-1900s, and it was not until the 1990s that the receptors to which cannabinoids interact within the human body were discovered, arousing the scientific community's awareness of and interest in these receptors and the endogenous substances that bind them.[40]

Today, there are many slang terms for marijuana including weed, herb, chronic, hash, pot, grass, bud, ganja, and Mary Jane. Its main psychoactive ingredient, THC, is found in resin produced by the leaves and buds primarily of the female marijuana plant. The plant also contains more than 500 other chemicals including more than 100 compounds that are chemically related to THC and are together called cannabinoids.

Endocannabinoid System

The endocannabinoid system is composed of endogenously produced cannabinoids, cannabinoid receptors, and the enzymes that regulate the production and destruction of cannabinoids.[41] Two cannabinoid receptors have been identified to date, CB1 and CB2, both G protein–coupled receptors. The CB1 receptor, first cloned in 1990, is found primarily in the central nervous system on axons and nerve terminals,[42,43] whereas the CB2 receptor, derived from a promyelocytic line in 1993, is expressed largely on immune cells.[43,44] Cannabinoid receptors primarily affect actions via inhibition of adenylyl cyclase and MAP kinase activation.[45]

Exogenous cannabinoids, the 2 most clinically relevant of which are THC and CBD, act on CB1 and CB2 receptors. Agonists at CB1 receptors will cause decreased neuronal signaling across the synapse in which the receptors are activated. The downstream effect of this diminished neuronal signaling can be increased release of certain neurotransmitters if the depressed neuron functions in a regulatory capacity. This effect has been demonstrated in a rat model in which THC increases acetylcholine release in the hippocampus; acetylcholine, glutamate, and dopamine in the prefrontal cortex; and dopamine in the nucleus accumbens; likely by this mechanism, THC generates psychoactive effects, reward signals, and polyphagia.[38] The overall characterization of the mechanism of THC is more complex than originally thought, as emerging evidence suggests that THC can act as an agonist and antagonist at CB receptors, depending on the receptor density. Therefore, there is heterogeneity in the effects of THC in various neuronal systems.

Cannabidiol has overall low affinity of CB1 and CB2 receptors, but has been shown to have activity at very low concentrations. It has been established that CBD acts as an inverse agonist at CB1 receptors[46,47] and theoretically at CB2 receptors as well, thus providing a mechanism for the observed anti-inflammatory properties of CB2.[48] Understanding the mechanism underlying CBD remains an area of active research and is especially relevant to the clinician as patients increasingly utilize CBD-based products for therapeutic effect.

COMMON FORMS OF MARIJUANA AND METHODS OF USE

Inhaled Marijuana

This is the fastest method for THC to enter the systemic circulation and includes smoking, vaporizing, and dabbing (Table 1). Of these, smoking provides a rapid onset (1–3 minutes) and short duration (1–3 hours) of symptoms, which results in a lesser chance of overconsumption.[49] While smoking has historically been most popular, it is not an efficient method as lighting marijuana destroys some of the medical compounds, and carcinogens are released along with particulate matter. Vaporizing uses a low-temperature electronic portable cigarette or desktop unit to heat marijuana until the plant oils are vaporized and, as with smoking, has a quick onset and short duration.[49] Dabbing consists of using small quantities of highly potent cannabis concentrates that are made from hash oil and vaporized, which may be easier to overconsume.

Oral or Gastrointestinal Absorption of Marijuana

Oral membrane absorption includes drops, tinctures, sprays, lollipops, or breath strips and can take approximately 20 minutes before symptoms occur and can last 1 to 3 hours[49] (Table 1). In contrast, gastrointestinal absorption includes edibles, candies, drinks, snacks, and capsules that require digestion before an effect is felt, which can range from 30 to 90 minutes after consumption, lasting 6 to 8 hours[49] (Table 1). Of these, edibles are very popular because they are palatable and discreet, and effects can for last hours. Because of the delay in onset of symptoms, these methods lead to a higher likelihood of overconsumption.[49]

Skin Absorption of Marijuana

There are 2 types of marijuana infused skin products: (1) topicals, which work on the area of skin applied, and (2) transdermals, which are absorbed into the bloodstream (Table 1). Topicals are nonpsychoactive and include balms, salves, lotions, liniments, and bath soaks, which do not enter the bloodstream and thus do not result in a positive urine drug screen. Their onset of action is 15 to 30 minutes after application and effects can last for 3 to 6 hours.[49] Transdermals include patches and gels, which are felt 15 to 30 minutes after applying and normally last from 6 to 8 hours. Patches used are time-released, measured doses of which can be cut into smaller pieces if a lower dose is desired.[49]

Suppositories

These are made from oils and waxes that can be applied rectally or vaginally (Table 1). Vaginal suppositories have similar onset times to oral mucus membrane absorption (20

minutes) and last approximately 3 to 6 hours.[49] In contrast, rectal suppositories are not as readily absorbed into the bloodstream and thus are less psychoactive.[49]

PREVALENCE AND PERCEPTIONS OF PRENATAL MARIJUANA USE

Research on the prevalence of marijuana use by pregnant women is limited. The prevalence of self-reported prenatal marijuana use is 2% to 5% in most studies, but is up to 15% to 28% among young, urban, and socio-economically disadvantaged women.[4,50–52] Of note, it is reported that 48% to 60% of marijuana users continue their use during pregnancy.[3–5] Data from the 2014 National Survey of Drug Use and Health suggest that 3.85% of pregnant women between the ages of 18 and 44 years engaged in past-month marijuana use compared with 2.37% in 2002.[53]

A statewide Colorado survey sponsored by the Centers for Disease Control and Prevention, Pregnancy Risk Assessment Monitoring System, was performed in 2014, after marijuana legalization, asking new mothers questions about marijuana use during the pregnancy and postpartum.[54] The results of this survey were notable for 11 % of new mothers reporting the use of marijuana shortly before conception and 6% using it during their pregnancy.[54] Maternal use was found to be highest among women aged 20 to 24 years (13%) compared with 25 to 34 years old (4%) and 35 years or older (3%).[54] Additionally, women were also more likely to use if they had less than a 12th-grade education (16%) compared with women with some college background (4%).[54] Race and ethnicity did not appear to affect the prevalence of maternal use. In general, marijuana use preconception was statistically higher (11.2%) than during pregnancy (5.7%) or while breastfeeding (4.5%).[54]

This high frequency of use is partly due to a perception that marijuana use is relatively safe during pregnancy. The National Survey on Drug Use and Health, a nationally representative survey on substance use, was performed from 2005 through 2015 and noted that 17% of pregnant nonusers and 65% of pregnant marijuana users reported no anticipated health risk with marijuana.[55] This perception of safety is, to some extent, secondary to the expanding legalization and from erroneous interpretations of the limited and confounded data regarding perinatal outcomes.

MARIJUANA TESTING

Marijuana testing is used to detect the presence of THC or its metabolites, most often THC-COOH, because it stays in the body longer than THC itself, to indicate marijuana or prescription cannabinoid use. Most often, this is performed by urine or serum testing, but saliva and hair can be tested as well. Saliva is more commonly used for workplace testing and is collected by an absorbent pad or swab between the lower cheek and gums. Positive screening tests for marijuana are presumptive and have the potential for false-positive results; thus, it is recommended that they be confirmed with a second test such as gas chromatography/mass spectrometry and liquid chromatography-tandem mass spectrometry.

Newborn testing can be performed using umbilical cord homogenate, meconium, serum, or urine. The umbilical cord homogenate can be used after the second trimester and is easier to collect, but less sensitive, than meconium.[56]

MARIJUANA PHARMAKOKINETICS

It has been previously demonstrated in both humans and animal studies that THC rapidly crosses the placenta and that concentrations in fetal blood closely resemble those in maternal blood, although fetal plasma concentrations are lower than maternal concentrations in some species.[11,32,57,58] The metabolites 11-OH-THC and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol both cross the placenta, but with less efficiency than THC.[32,58] However, as most of these studies were performed in the 1970s and 1980s when the potency of marijuana was much less, currently there are very limited contemporary data regarding the quantity transferred in relation to the concentration of THC in the marijuana, the frequency of maternal use, or the amount in maternal serum.

In response to the lack of scientific research regarding an emerging public health concern, especially in vulnerable populations such as pregnant women, the National Academies of Sciences, Engineering, and Medicine created a committee to investigate the current state of evidence regarding the health effects of marijuana and to identify and prioritize critical gaps in research.[29] The committee's findings and suggestions include the need to investigate the pharmacokinetic and pharmacodynamic properties of THC only, at different concentrations, including dose-response relationships.[29,59] Prior marijuana pharmacokinetic studies have primarily focused on nonpregnant adults smoking marijuana, with few reports on newer marijuana product use during pregnancy.[25–28] Previous rodent and rabbit studies performed in the 1960–1980s have provided some information on the pharmacokinetics and placental transfer of THC, but at a lower historical dose.[25,60–71] In the rat, it has been shown that following maternal ingestion THC concentrations in fetal blood are approximately 1/10th of maternal concentrations[11,37] compared with one-third after intravenous or inhaled THC delivery.[57,58]

It has been shown that marijuana can affect the placenta's normal transport mechanisms and physiology.[72] In dizygotic twins, it has been observed that the placenta contributes to the variability of fetal marijuana exposure.[73] Another study demonstrated that short-term exposure to CBD can enhance the permeability of the placental barrier to pharmacologic agents and recreational substances, thus potentially increasing fetal exposure to other agents.[74] Others, however, have demonstrated that prenatal human exposure is associated with diminished blood flow supplying the placenta.[52,75] Overall, the critical variables in the effects of prenatal marijuana use include the duration and timing of exposure, the overall magnitude of exposure, and the extent to which the fetus and the fetal brain are exposed to THC after maternal use. It is also possible that the route of exposure (ie, oral, inhalation, different methods of smoking) impacts fetal toxicity because the absorption pathways of smoked and edible marijuana products differ greatly. If orally administered, THC absorption is usually greater than 90% and not affected by formulation,[76] but the bioavailability is limited to less than 20%[77] secondary to significant first-pass hepatic metabolism. In contrast, when marijuana is smoked, it avoids first-pass hepatic metabolism, but THC is inadvertently lost in sidestream smoke, the cigarette butt, and from pyrolysis, resulting in low THC absorption and highly variable bioavailability, ranging from 2% to 56%.[78,79]

EFFECTS OF MARIJUANA IN PREGNANCY

The existing research on marijuana and pregnancy, including animal studies, dates largely from an era when marijuana products were less potent and popular.[31,32,34,35,80–82] In addition, human studies of maternal marijuana use are mostly limited by a retrospective or observational design, rely primarily on patient self-report, and are confounded by polysubstance abuse and small sample sizes, precluding determination of a causal effect specific for THC.[2, 24] Women also tend to underreport their marijuana use, up to 60% to 70%, and there is no biological validation for self-reporting.[24,29]

Maternal smoking, nutritional inadequacy, and medication or illicit drug use can all have a synergistic effect on marijuana exposure and often confound human studies of placental impairment and fetal development. Animal models, however, can allow for experimental manipulation and can minimize confounders and subject variability. Studies of THC in rats have demonstrated structural brain changes, specifically in the nucleus accumbens,[83] which have also been reported in humans.[84] Compared with lower-order-species animal models studying the effects of prenatal marijuana exposure, the nonhuman primate (NHP) is advantageous because of its similarities in fetal development and placental structure and function.[85,86] Additionally, the NHP has a similar plasma disposition of THC and metabolites to humans, making it a useful translational model.[87] Nonhuman primate studies of prenatal marijuana have focused on the effects of acute THC dosing in the third trimester[32] or the effects of chronic THC on fetal growth using only standard ultrasound fetal biometry in vivo[88] and an intravenous dosing route. An NHP study reported increased pregnancy loss (3 miscarriages and 1 term stillbirth) in 5 animals when daily THC was administered intravenously starting in the middle of the first trimester.[88] However, additional animal studies are needed with contemporary THC dosing to better assess the effects of maternal marijuana use.

Stillbirth and Miscarriage

Human studies of illicit drug use in pregnancy have reported associations between substance use and pregnancy loss, although early investigations of marijuana use alone failed to demonstrate a statistically significant association between stillbirth or early miscarriage and prenatal marijuana exposure.[14,15,89]

The largest contemporary study addressing this potential association is from the Stillbirth Collaborative Research Network, which studied the impact of illicit drug use and smoking on stillbirth.[18] This case-control study included 663 stillbirth deliveries, from 5 different clinical sites over 2 years, with cord homogenate toxicology and maternal cotinine assays performed at the time of delivery. Marijuana use, as evidenced by tetrahydrocannabinolic acid–positive umbilical cord homogenate screening, was significantly associated with stillbirth (odds ratio [OR], 2.34; 95% confidence interval [CI], 1.13–4.81), although this effect was partially confounded by concurrent maternal tobacco use.[18] The use of assay-proven marijuana use, as opposed to relying on self-report, is a strength of these data, although there were racial, ethnic, and gestational age differences between cases and controls who did or did not undergo toxicology testing.[18] Additionally, like many prior studies, the effect of marijuana on stillbirth was also partially confounded by tobacco use.[18]

Another more recent study from 2018 examining tobacco and marijuana couse in an urban, university hospital population also reported an association between marijuana use and stillbirth and miscarriage.[90] This study compared patients using tobacco only, marijuana only, and couse of tobacco and marijuana.[90] Patient-reported substance use was confirmed with urine and hair samples.[90] The authors found that marijuana-only users had 12 times greater odds of miscarriage or stillbirth as compared with nonusers.[90] Conversely, a retrospective cohort study published in 2015, which excluded polysubstance users and used a stratified logistic regression to account for concurrent tobacco use, failed to demonstrate an association between marijuana products and stillbirth. This study was, however, underpowered to detect such an association.[91]

The mechanism underlying the possible association between stillbirth and marijuana use in pregnancy has yet to be fully elucidated. However, a recent study on the effect of THC on human trophoblastic tissues suggests that THC alters both cytotrophoblast and syncytiotrophoblast cellular remodeling. In the context of placental development, the antioxidant effects of THC may inhibit normal placental growth and development.[92] Overall, the existence of an association between marijuana use in pregnancy and stillbirth or miscarriage remains unclear, but in light of recent data and investigations into the effects of marijuana on placental tissue, it cannot be definitively ruled out.

Preterm Labor and Preterm Birth

A previous large systematic review by Gunn et al[93] assessing the effects of marijuana use during pregnancy on maternal and fetal outcomes found a decrease in gestational age (measured by weeks) and increased odds of a preterm delivery (pooled OR, 1.29; 95% CI, 0.8–2.08). In contrast, other studies have reported no association between maternal marijuana use and shortened gestation[50,94]; Gray et al[94] examined 86 infants and found a median estimated gestational age at delivery of 39 weeks ($P = 0.685$) for both exposed and nonexposed infants. Two prior studies, Dekker et al[95] and Leemaqz et al,[96] similarly noted an increased risk of spontaneous preterm birth with marijuana use during pregnancy (adjusted ORs [ORs], 2.34 [95% CI, 1.22–4.52] and 2.28 [95% CI, 1.49–3.6]; $P < 0.001$, respectively).

Fetal Growth Restriction and Small for Gestational Age

Several studies have found that in utero marijuana exposure is associated with a significant decrease in birth weight[15,93,94] ranging from a 84- to 256-g difference, whereas Schempf and Strobino[51] reported no difference after adjusting for other maternal drug use. Studies have found no significant association between prenatal marijuana use and neonatal head circumference or birth length.[93] A prior study by Janisse et al[97] examined 3164 pregnant, urban black women from entry to prenatal care through delivery and assessed substance use through patient self-report. The result of this study was that heavy marijuana use alone was associated with a reduction in birth weight, but not with increased preterm delivery.[97]

Neonatal Effects

Although a prior systematic review noted an increased risk of neonatal intensive care unit admissions (pooled OR, 2.02; 95% CI, 1.27–3.21) associated with prenatal marijuana

exposure, there was no association with infant Apgar scores at 1 and 5 minutes, jaundice, resuscitation, respiratory distress syndrome, intubation following delivery, hypoglycemia, and sepsis.[93] Similarly, another large study, by Warshak et al,[91] of 4892 women who used marijuana in pregnancy also noted an increased risk of neonatal intensive care unit admissions (aOR, 1.54; 95% CI, 1.14–2.07). In both studies, there was no reported association between maternal marijuana use and chromosomal or fetal anomalies.[91,93] However, van Gelder et al[50] examined the association between marijuana use in pregnancy from 1 month prior to conception through the first trimester and 20 selected anomalies in a total of 13,859 infants exposed to prenatal marijuana and compared this with 6556 control infants. The authors noted an increased risk of anencephaly (aOR, 2.2; 95% CI, 1.3–3.7), esophageal atresia (aOR, 1.4; 95% CI, 0.8–2.4), and diaphragmatic hernia (aOR, 1.4; 95% CI, 0.9–2.2) and a nonsignificant increase in gastroschisis (aOR, 1.2; 95% CI, 0.9–1.7).[50]

EFFECTS OF PRENATAL MARIJUANA USE AND NEWBORN AND LATER CHILDHOOD OUTCOMES

There is a significant interest in long-term effects of in utero marijuana exposure given the high prevalence of prenatal marijuana use, as it is the most frequently used substance in pregnancy both recreationally and for alleviation of morning sickness. Prior human research has demonstrated that some babies exposed to prenatal marijuana use will display altered responses to visual stimuli, increased trembling, and a high-pitched cry, which could indicate problems with neurological development.[98] Additionally, school-aged children born to mothers who used marijuana in pregnancy are more likely to show gaps in problem-solving skills and memory, have increased depressive and anxiety symptoms, and decreased ability to remain attentive.[99,100] Later in adolescence, increased delinquency and increased likelihood of early age at onset of marijuana use (defined as by 15 years old) have been observed.[101,102] However, the literature regarding the effects of maternal marijuana use on later outcomes in the offspring is largely limited and largely consists of 3 main cohort studies that aimed to assess the long-term outcomes of prenatal marijuana exposures. However, these 3 studies were conducted from 1970 to 2001, and the potency of marijuana has consistently risen over time since 1995.[103] Therefore, the adverse effects of prenatal exposure to marijuana reported in these studies may be different in offspring of mothers who are using marijuana in pregnancy today. Overall, there is currently insufficient evidence to establish an association between maternal marijuana use and later outcomes in the offspring including sudden infant death syndrome, cognition, academic achievement, and later substance abuse.[29]

Ottawa Prenatal Prospective Study

The first of these studies was a longitudinal study from Canada designed to assess the association between socially used drugs consumed during pregnancy and the effects on offspring.[104] Data collection was by interview each trimester regarding drug use while pregnant. This study included 689 women, mostly middle-class and low-risk, of which 140 women reported some use of marijuana, or smoking at least 16 mg of nicotine daily, or drinking greater than 0.85 oz of alcohol daily.[104] The control group consisted of 50 randomly selected women who did not use any substances in pregnancy. These children

were followed during the neonatal period, yearly until 6 years of age, and at specific preidentified time points through adolescence until 18 to 22 years of age. Offspring were evaluated by age-appropriate standardized global measurements of IQ and neuropsychological tests to assess language development, memory, visual/perceptual functioning, components of reading, and sustained attention across different developmental time periods.[29,105] In the neonatal period, investigators observed decreased visual habituation, increased tremors and startles, and more hand-to-mouth behavior.[104] During early childhood, they found no adverse effects on IQ or on scales assessing mental, motor, behavioral components, poorer abstract/visual reasoning at 3 years of age and decreased performance on verbal and memory subscales at 4 years of age.[104] By age 6 years, children were found to have poorer sustained attention and higher parental ratings for hyperactivity/impulsivity.[104] From ages 6 to 9 years, children had poorer scores on tasks assessing sustained attention, visual perceptual functioning, language comprehension, and distractibility.[104] Later on, between 9 to 12 years of age, no association was found with full-scale IQ or composite IQ, but poorer scores on tasks assessing "higher-order" functioning or, more specifically, executive functioning, and an effect on impulse control, visual analysis, and hypothesis test results.[104] In adolescence, there was no association observed with overall IQ, but decreased concentration as well as impairment of visual memory, analysis, and integration was detected.[104] Then, as young adults, ages 18 to 22 years old, decreased response inhibition was noted.[104] Of the subjects studied, 35 (aged 18–22 years) underwent brain functional magnetic resonance imaging to better assess the long-term consequences of in utero marijuana exposure (16 were prenatally exposed to 0.33–53 joints/wk with a mean of 8.27 joints/wk). These individuals performed multiple executive functioning tasks while in the scanner that identified significantly more brain activity in the prenatally exposed group compared with the nonexposed group.[106] This suggests that the prenatally exposed group needs a compensatory response whereby either additional brain regions are required to perform the tasks or more activity in typically activated regions is necessary to perform the task. In addition, there was altered brain activity in involved in working memory and response inhibition in exposed subjects.[106,107]

Overall, this study found that prenatal marijuana exposure does appear to have neurocognitive effects on offspring, but that these effects vary at different stages of the exposed child's life. There does not appear to be any correlation with overall IQ, which in contrast is found to be negatively impacted in offspring exposed to tobacco in utero. As children exposed to marijuana in utero age, they tend to have lower scores on tasks used to assess executive functioning. While precursors of executive functioning are present in infants and toddlers, prefrontal functioning in areas such as selective attention, information integration, and verbal fluency tends to not be apparent until a child is school-aged.[104] Therefore, it is premature to conclude that the absence of significant neurocognitive effects in the neonatal and early childhood period indicates lack of negative effects from in utero marijuana exposure on a child's long-term neurologic development. Rather, the effect of the exposure becomes more apparent as a child ages and the adverse effects on the neurologic constructs related to executive function begin to manifest.

Maternal Health Practices and Child Development Study

Another longitudinal cohort focused mainly on prenatal alcohol and marijuana exposure in women who were of lower socioeconomic status and comprised approximately half white and half African American ethnicity.[107] A total of 1360 women from a hospital-based prenatal clinic were interviewed, of which 30% reported marijuana use in the first trimester.[107] This study found that prenatal marijuana exposure negatively impacted sleep continuity and organization at birth through 3 years of age. At age 3 years, children born to mothers who used marijuana had lower scores on verbal reasoning and short-term memory. By age 6 years, first-trimester marijuana exposure was associated with lower verbal reasoning scores, second-trimester exposure was associated with lower scores on the composite short-term memory and quantitative reasoning scores, and third-trimester exposure predicted lower scores on quantitative reasoning measures.[107] At age 10 years, exposed offspring were noted to have higher rates of depression and anxiety, impulsivity, hyperactivity, inattention, and memory deficits.[107] The observed deficits in this study, after adjusting for maternal confounders, were not found to be linear, but rather associated with heavy use (1 or more marijuana joints per day). Similar to OPPS, the Maternal Health Practices and Child Development Study demonstrated deficits in executive function that persisted into late adolescence and young adulthood in children of marijuana users.[107]

Generation R Study

A third, and the most recent, longitudinal study was based in Rotterdam, the Netherlands, and studied children of a multiethnic population of 7452 women from fetal life until adulthood.[14] This study, adjusting for confounding variables, reported reduced fetal growth starting in the second trimester and overall lower birth weight in infants exposed prenatally to marijuana.[14] At 18 months, exposed female infants were found to have more aggression and inattention, but by 30 and 36 months there was no difference found in nonverbal cognition or vocabulary development between exposed and nonexposed children.

Possible Basis for Observed Long-term Outcomes

Cannabinoid receptors (specifically CB1) are abundant in prefrontal cortex, anterior cingulate, basal ganglia, amygdala, hippocampus, and cerebellum, and activity in these receptors by naturally occurring endogenous cannabinoids plays an important role in cell proliferation, neurogenesis, and migration. In addition, current research has shown that cortical neuronal networks undergo maturational refinement as an individual ages until late adolescence when executive functioning abilities are reaching their potential. Exogenous cannabinoids are able to cross the placental barrier and can interfere with the development of the widespread endocannabinoid system within the brain and limit executive functioning in the future.[106] Both CB1 and CB2 receptors are located on the myocardium, coronary and cerebral vasculature, and on cardiomyocyte as well, and therefore exogenous cannabinoid exposure in utero may have cardiovascular effects as well.[107] The literature on whether prenatal marijuana exposure affects early physical development varies, and strong evidence that marijuana has a long-term negative impact on physical growth or maturation is lacking.[87]

MARIJUANA USE AND BREASTFEEDING

As the main psychoactive ingredient of marijuana, THC, is 99% protein bound and highly lipid soluble and has a low molecular weight; it is transferred into human breast milk and stored in lipid-filled tissues such as the fetal brain.[108] Long-term maternal use has been shown to lead to fetal accumulation.[109] A prior NHP study performed in 1976 determined that 0.2% of the THC ingested by the mother was detected in breast milk.[110] Thus, if a mother smokes 1 to 2 marijuana cigarettes a day, a nursing infant may ingest approximately 0.01 to 0.1 mg of THC daily. In humans, it was also previously reported in 1982 that the THC concentration in maternal breast milk was 8.4 times higher than in plasma.[109]

Overall, there is also little known regarding the frequency of marijuana used by women who are breastfeeding. A recent cross-sectional study of marijuana use from Colorado reported a 5.0% (95% CI, 4.1%–6.2%) prevalence of early postnatal marijuana use among breastfeeding women.[111] Another survey from Colorado, of women attending the Special Supplemental Nutrition Program for Women, Infants, and Children program, found that among all marijuana users (past, ever, current), 18% had used marijuana while breastfeeding.[112]

This prevalence is concerning because a prior study by Perez-Reyes and Wall[109] suggests that moderate amounts of THC are present in breast milk when a nursing mother uses marijuana and that this is absorbed by the infant, as evidenced by the presence of THC in infant stool. Other studies have shown that THC concentrations in breast milk peak at 1 hour postinhalation and remain in breast milk for up to 6 days after marijuana usage.[113,114] Although it is well established that THC can accumulate in human breast milk and reach high concentrations, its effect on exposed infants remains uncertain. Theoretically, because an infant's brain is continuing to develop, THC consumed in breast milk could affect brain development.

Little is known regarding the direct developmental effects of exposure to marijuana through nursing in part because these studies are often confounded by other drug or alcohol use.[115] A prior study demonstrated that exposure to THC through breast milk in the first month of life can result in decreased motor development at 1 year of age.[115] Astley and Little[115] examined the relationship between marijuana exposure via breast milk and infant motor/mental development at 1 year of age. This study utilized prospectively gathered data from a cohort of 400 predominantly white, middle-class pregnant women and evaluated them for tobacco, alcohol, and drug use. It identified 68 infants with postnatal marijuana exposure that were matched to nonexposed infants by prepartum and postpartum tobacco and alcohol use. A multivariate regression analysis demonstrated that daily infant exposure to marijuana via breast milk was associated with a 14-point (±5-point) decrease in infant motor development scores at 1 year of age after controlling for concurrent maternal tobacco, alcohol, and cocaine use.[115] However, this study was limited by confounding from prenatal marijuana exposure and a lack of long-term follow-up.[115]

Maternal marijuana use while breastfeeding can also affect breastfeeding patterns among marijuana users. Crume et al[111] showed that there is not a statistically significant decrease in

breastfeeding initiation among marijuana users. However, in that study, 64.4% (95% CI, 54.9%–72.9%) of women who reported perinatal marijuana use breastfed for 9 weeks or more, which was lower than the rate of 78.3% (95% CI, 76.2%–80.3%) in women who did not use marijuana during pregnancy ($P = 0.02$). This is important because breastfeeding is recognized as the ideal feeding method for infants because of the numerous short- and long-term benefits for both mother and child. Future studies are needed to establish whether the association between perinatal marijuana use and shorter duration of breastfeeding is due to breastfeeding failure or intentional breastfeeding discontinuation, given that there are data suggesting cannabinoids have an inhibitory effect on prolactin secretion.[116] Given the limited evidence surrounding breastfeeding while actively using marijuana, at this time, nursing mothers are discouraged from using marijuana.[2]

PERCEIVED BENEFITS

There are many perceived benefits for marijuana use in pregnancy, including for postpartum depression or back pain, but most commonly it is used for nausea and vomiting. Although medications, diet, and lifestyle modifications are among recommended interventions for nausea and vomiting,[2] some pregnant women choose to use marijuana to self-medicate their nausea and vomiting symptoms because it is felt that maternal marijuana use has very little harm.[117,118] In addition, online marijuana and marijuana dispensaries are recommending marijuana as a harmless and effective treatment for nausea and vomiting in pregnancy.[118,119] A recent cross-sectional statewide study from Colorado used a mystery caller approach to contact 400 dispensaries to characterize recommendations given to a pregnant woman in the first trimester regarding the use of marijuana products for nausea.[119] It was determined that nearly 70% of Colorado marijuana dispensaries contacted recommended marijuana products to treat nausea in the first trimester, with few dispensaries encouraging discussion with a health care provider without prompting.[119] Another recent study analyzed online media items from 2015 to 2017 to characterize how scientific information about prenatal and postpartum marijuana use was presented in online media content and to assess how media portrayed risks and benefits of such marijuana use.[118] Online media content was found using the Google Alerts function to simulate the experience of an individual searching for information online. This study found that 10% of media portrayed the benefits of prenatal or postpartum marijuana as greater than the risks, and almost a third mentioned marijuana use for treatment of nausea and vomiting in pregnancy.[118]

PROFESSIONAL GUIDELINES FOR USE OF MARIJUANA IN PREGNANCY

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists has published guidelines recommending that obstetrician-gynecologists counsel women against using marijuana while trying to get pregnant, during pregnancy, and while they are breastfeeding.[2] The American College of Obstetricians and Gynecologists Committee Opinion states that there are insufficient data to evaluate the effects of marijuana use on infants during lactation, and in the absence of adequate data, marijuana use during lactation and breastfeeding should be

discouraged until future studies can delineate clinical scenarios in which marijuana-exposed breast milk remains preferred for infant consumption.[2]

American Academy of Pediatrics

The American Academy of Pediatrics (AAP) recognizes the paucity of data to guide clinician recommendations. A statement by the AAP in 2018 suggests that marijuana use should be discouraged during breastfeeding, given insufficient evidence to evaluate the effects of marijuana exposure on infant development. The AAP statement did not include recommendations regarding whether marijuana use should be considered a contraindication to breastfeeding, or whether expressed milk from mothers known to be using marijuana products should be used to feed premature infants.[120]

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention currently recommends against the use of marijuana in pregnancy because it can potentially result in adverse fetal development.[121]

INTERVENTIONS

There is a wide range of universal prevention programs for marijuana use, not specific to pregnancy, with overall insufficient evidence to support a direct benefit. The Substance Abuse and Mental Health Services Administration previously performed an extensive review of the literature, primarily focused on youth prevention, and organized types of intervention into the following groups: community level, school level, family level, peer level, and individual level.[122] The reviewed evidence supported using mass media to increase public concern about use and change normative perceptions, parental monitoring, and messaging about use and highlighted the importance of an individual's attitude toward use, perception of harm, motivational enhancement therapy, marijuana check-ups, and individual level programs to change norms.[122]

RECOMMENDATIONS FOR HEALTH CARE PROVIDERS

There is currently no recognized "safe" amount of marijuana in pregnancy. Thus, at present, it is recommended to avoid marijuana in pregnancy because THC crosses the placenta, and there are uncertain perinatal effects, including a possible increased risk for stillbirth, preterm birth, fetal growth restriction, and miscarriage. In contrast, THC is not felt to be associated with specific congenital anomalies. Currently, it is recommended that health care providers screen all women verbally for marijuana use at their intake for obstetrical care and consider rescreening later in pregnancy. Screening can be performed using the Cannabis use Disorder Identification Test—Revised, which consists of a series of 8 items; a score of 8 or more indicates hazardous cannabis use, and scores of 12 or more suggest a possible cannabis use disorder.[123] For patients who are high-risk, urine toxicology screening should be considered. Women who use marijuana and desire cessation should be referred to appropriate resources including substance-use programs. Overall, clinical care should not be otherwise modified (ie, growth ultrasounds, cervical length screening, and antenatal surveillance). At the time of delivery, marijuana screening questions should be used, and if maternal or newborn urine is

screened, positive results in the absence of reported maternal drug use should be confirmed by gas chromatography/mass spectrometry or liquid chromatography-tandem mass spectrometry. Alternative newborn testing includes meconium or umbilical cord sampling. Postpartum, it is recommended to avoid marijuana while breastfeeding because THC is passed to the neonate in breast milk, and there may be longer-term adverse effects on behavior and neurodevelopment. However, it is not currently recommended to withdraw lactation support if women are unable to abstain.

CONCLUSIONS

Overall, marijuana is gaining greater societal acceptance in part because of the changing legalization climate and messaging via social media regarding the safety of marijuana use during pregnancy. Combined with a fall in marijuana costs, even as drug potency continues to rise, secondary to expanding legalization,[124] this has contributed to the rapidly mounting prevalence in use. As prenatal marijuana use is becoming more commonplace, and there is little known on contemporary dosing, there is an urgent need for evidence-driven recommendations on the safety of use during pregnancy and lactation. It is crucial for pregnant women to understand what is known about both the adverse health effects and the potential therapeutic benefits linked to marijuana. Once prenatal effects are better identified and well characterized, patient education and antenatal surveillance strategies can be developed to minimize maternal, fetal, and neonatal morbidity and mortality, as well as to guide obstetricians in appropriately counseling women regarding prenatal marijuana use.

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TABLE 1

Summary of Different Modes of Cannabis Delivery

Method	Onset	Duration
Inhaled (vapor or smoke)	1–3 min	1–3 h
Oral (drops, lozenge, spray)	10–25 min	1–3 h
Ingested (capsules, edibles, drinks)	30–90 min	6–8 h
Topical (balms)	15–30 min	3–6 h
Transdermal (patch, gels)	15–30 min	6–8 h
Vaginal suppository	20 min	3–6 h